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Abstract

The invention relates to a nitroglycerin-containing hydrophilic aqueous pump spray in the claimed composition.

The spray according to the invention contains no CFC-containing propellant gases and is distinguished by excellent storage stability and dosage accuracy.

PATENTS ACT, 1964

COMPLETE SPECIFICATION

HYDROPHILIC AQUEOUS PUMP SPRAY CONTAINING NITROGLYCERIN

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Description

The invention relates to a hydrophilic aqueous pump spray containing nitroglycerin but no propellant gas and to the preparation thereof.

Nitroglycerin, also called glycerol trinitrate (GTN), is an agent for the treatment of attacks of angina pectoris. It is employed, inter alia, in emergency situations in which the pharmaceutical form must make a rapid onset of action possible.

The pharmaceutical forms employed for this specific indication, such as sublingual tablets or bitable capsules, have disadvantages. It is disadvantageous, inter alia, that the agent in this pharmaceutical form must, after intake, first be released and distributed before it is available in dissolved form for absorption. Furthermore, an unnecessary loss of time occurs on treatment of an acute attack when the pharmaceutical form first has to be taken out of the pack and blister.

To avoid the disadvantages of these pharmaceutical forms, in particular sprays containing GTN and propellant gas have been developed. The intention was, by spraying the agent-containing dose into the mouth, to ensure direct and rapid application of a solution of the agent onto a portion which is as large as possible of the oral mucosa which absorbs the agent GTN well. This is intended to reach a large area, which increases the rate of diffusion of the agent.

However, sprays containing propellant gas have

numerous disadvantages. The lower halogenoalkanes used as propellant gas have environmentally damaging effects. Associations have been suggested between the use of chlorofluorocarbons and the reduction in the ozone content of the upper layers of the atmosphere. This is why many countries place restrictions on the use thereof as propellant gas.

With regard to the indication for employing GTN-containing propellant gas sprays for treatment of acute attacks of angina pectoris, the propellant gases which are used have the disadvantage of having a drying effect. Since, however, the mouth always becomes dry during an attack of angina pectoris, the drying effect of the propellant gases is particularly disadvantageous.

Because of the substance-specific properties of GTN, many nitroglycerin-containing products which contain a vehicle system based on fats and oils have been described.

However, the disadvantage in this case is that these products must contain at least one preservative so that the fatty acids contained in the triglycerides do not become decomposed, oxidised or rancid. Additives of such types in pharmaceuticals are, however, undesirable not only per se but also in view of their possible ability to induce allergies.

Furthermore, lipophilic solvents prevent the agent GTN being distributed in the hydrophilic mucosa with the rapidity required in acute attacks of angina pectoris.

In the past, the amount of lipophilic solvents employed has been reduced to increase the availability of the agent in metering aerosols containing propellant gases. However, there was only a slight effect on the time needed for the level to rise, which can be measured from the maximum plasma concentration (c_{max}) and time of maximum concentration (t_{max}).

Although P.M. Dewland et al. [in Herz & Gefäße, 1, 536 - 544 (1987)] obtained higher c_{max} values (Tab. 1 loc. cit.) with a decreasing amount of the lipophilic constituents in three GTN sprays prepared with lipophilic solutions, there is no significant difference in t_{max}.

Another approach to increasing the availability of the agent is explained in DE 32 46 081.

In the formulation described in this document, the propellant gas content is increased to 60 - 95% of the components of the formula.

In this case, the increased propellant gas content results in a higher concentration of the agent in the involatile oily solvent.

However, it is still necessary for the pharmaceutical substance first to diffuse out of the oily agent solution into the mucosa. However, it is not possible in this way significantly to reduce the time needed for the level of agent to rise, which is important in the case of an attack. From the viewpoint of enhanced environmental consciousness, an increase in the propellant gas content is disadvantageous and thus to be avoided.

A qualitatively distinct improvement in sprays in

the case of attack is not possible while retaining lipophilic solvents in metering aerosols containing propellant gas.

Another approach to rapid distribution of the agent into the hydrophilic mucosa is the use of a solvent which mixes with the aqueous mucosa. In this case the spray formulation must take into consideration that this solvent sufficiently desensitises the agent and, moreover, can be handled safely under production conditions in industry.

US Patent 3,155,574 describes a nitroglycerin spray formulation, containing propellant gas, for inhalation which is based on hydrophilic solvents, containing the agent GTN, 1,2-propanediol and absolute ethanol.

Inhalation is unnecessary because GTN is sufficiently absorbed through the oral mucosa, which increases the bioavailability in the same way as the absorption by reducing the first pass. Furthermore, it is extremely difficult for the patient to inhale in the case of an attack.

Investigations by H. Laufen et al. in Therapiewoche 34, 963 - 970 (1984) produced the result that in the case of a hydrophilic formula both the appearance of the agent in the blood and the amount of absorbed substance is more rapid and larger, respectively, than with lipophilic-based GTN sprays. However, the composition of the preparation and the metering system were not published.

EP 0 310 910 now describes a hydrophilic GTN

spray formulation which contains no chlorofluorocarbons and, apart from the agent, contains merely ethanol and water as solvents.

A disadvantage of this formulation is the lack of desensitisation of GTN. If solvent evaporates, in which case there is a reduction in the ethanol content in particular, then GTN precipitates as oily phase in the form of drops at the bottom of the bottle. At the same time, the above formulation necessarily uses GTN dissolved in ethanol, with the disadvantage of the flammability and danger of this raw material.

DE-A 39 22 650 describes as subject-matter of the invention a nitroglycerin-containing aerosol product which contains no propellant gas and consists of the agent GTN and 51 - 90% of one or more aliphatic alcohols with 2 - 4 carbon atoms and 10 - 49% of polyalkylene glycols or 1 - 3-hydric alcohols having 2 - 8 carbon atoms. The metering system used was not stated.

Furthermore, the high content of one or more aliphatic alcohols with 2-4 carbon atoms is a disadvantage in this formulation. The degree of evaporation of the alcohol and the volatility of the components of the formula from commercially available metering pumps is high, so that the composition changes after the spray has not been used for a long time, and a composition which did not correspond to the pharmaceutical formulation originally present in the storage vessel is used in the case of an attack. Finally, the high alcohol content is also a disadvantage from the economic viewpoint because

alcohol is a costly raw material.

Up to 49% polyalkylene glycols are also used in the formulation. However, whenever possible, polymeric vehicles should not be used in pharmaceutical preparations because they contain impurities such as initiator molecules, di- and tripolymers and catalyst residues. These impurities have unacceptable physiological effects.

In addition, the said GTN-containing spray formulations of the prior art have the disadvantage of delivering non-uniform amounts and agent concentrations per puff.

It is an object of the invention to eliminate the disadvantages of the prior art and provide a nitroglycerin-containing hydrophilic aqueous pump spray which contains no propellant gases and ensures a therapeutically effective blood level in the shortest possible time even after a long period of disuse or repeated use, and a process for the preparation thereof.

It has now been found, surprisingly, that a spray preparation of the composition according to the invention, composed of 0.15-0.50% by weight glycerol trinitrate, 24.50-24.85% by weight ethanol, 32.00% by weight propylene glycol and 43.00% by weight purified water, adjusted to pH 3-6, has an extremely beneficial pharmacokinetic behaviour for treatment in case of attacks of angina pectoris, with a rapid increase in the level and high bioavailability, and with the preparation being extremely stable chemically. Even after a long period of disuse or repeated use taking place at short time inter-

vals, a composition corresponding to that of the pharmaceutical preparation is ensured. The composition needs no preservatives, despite the water, owing to its defined content of alcohols. This represents another advantage of this formulation because of the increases in allergisation.

The spray preparation advantageously contains 0.30% by weight nitroglycerin, 24.70% by weight ethanol, 32.00% by weight 1,2-propylene glycol and 43.00% by weight purified water, adjusted to pH 6.0.

The spray preparation preferably contains 0.40% by weight nitroglycerin, 24.60% by weight ethanol, 32.00% by weight 1,2-propylene glycol and 43.00% by weight purified water, adjusted to pH 6.0.

The preparation according to the invention can, because of its relatively low vapour pressure defined by the composition according to the invention of its components, be employed with pump atomiser metering systems. This ensures that the advantage known per se from the CFC-containing nitroglycerin sprays, such as the reliable dosage irrespective of the period of disuse after the last use, is not lost.

One embodiment of the spray according to the invention is adjusted to pH 6 and has the following composition:

Glycerol trinitrate	0.30 %
Ethanol	24.70 %
1,2-propylene glycol	32.00 %
purified water	43.00 %

This preparation meets the pharmaceutical quality requirements because of its qualitative and quantitative composition of the mixtures. Even at customary winter temperatures, no glycerol trinitrate separates out in the cold.

The spray formulation according to the invention can be prepared using the processes and technologies customary in the preparation of pharmaceuticals.

The invention therefore also relates to a process for preparing the spray formulation according to the invention, which is characterised in that, in a manner known per se, 0.15-0.50% by weight glycerol trinitrate, 24.50-24.85% by weight ethanol, 32.00% by weight 1,2-propylene glycol and 43.00% by weight purified water are mixed together, and the resulting solution is dispensed into appropriate primary packs containing metering pumps provided with spray heads.

According to an expedient embodiment of the process according to the invention, 0.30% by weight nitroglycerin, 24.70% by weight ethanol, 32.00% by weight 1,2-propylene glycol and 43.00% by weight purified water are mixed, and the resulting solution is adjusted to pH 6.0 and introduced into suitable primary packs.

According to another advantageous embodiment of the process according to the invention, 0.40% by weight nitroglycerin, 24.60% by weight ethanol, 32.00% by weight 1,2-propylene glycol and 43.00% by weight purified water are mixed, and the resulting solution is adjusted to pH 6.0 and introduced into suitable primary packs.

Preparation

Example 1

a) 0.600 g of a glycerol trinitrate solution containing propylene glycol, with the composition 30 mg of glycerol trinitrate and 570 mg of 1,2-propylene glycol, were mixed with 2.50 g of ethanol, 2.630 g of 1,2-propylene glycol and 4.300 g of purified water and stirred until homogeneous. Subsequently 0.1 N hydrochloric acid was added dropwise until the pH was adjusted to 6.

The resulting solution was filtered through a PVDF filter (pore size 0.22 µm) supplied by Millipore. The solution was then introduced into a brown glass bottle onto which a metering pump with spray head was screwed.

b) Alternatively, the solution can be introduced into an aerosol glass bottle onto which a metering pump with spray head is crimped.

Example 2

a) 0.600 g of an alcoholic glycerol trinitrate solution, with the composition 30 mg of glycerol trinitrate and 570 mg of ethanol, were mixed with 1.900 g of ethanol (Merck), 3.200 g of 1,2-propylene glycol and 4.300 g of purified water and stirred until homogeneous. Subsequently 0.1 N hydrochloric acid was added dropwise until the pH was adjusted to 6. The resulting solution was filtered through a PVDF filter (pore size 0.22 µm) supplied by Millipore. The solution was then introduced into a brown

glass bottle onto which a metering pump with spray head was screwed.

b) Alternatively, the solution can be introduced into an aerosol glass bottle onto which a metering pump with spray head is crimped.

Example 3

a) 0.800 g of an alcoholic glycerol trinitrate solution, with the composition 40 mg of glycerol trinitrate and 760 mg of absolute ethanol, were mixed with 1.700 g of ethanol (Merck), 3.200 g of 1,2-propylene glycol and 4.300 g of purified water and stirred until homogeneous. Subsequently 0.1 N hydrochloric acid was added dropwise until the pH was adjusted to 6. The resulting solution was filtered through a PVDF filter (pore size 0.22 μm) supplied by Millipore. The solution was then introduced into a brown glass bottle onto which a metering pump with spray head was screwed.

b) Alternatively, the solution can be introduced into an aerosol glass bottle onto which a metering pump with spray head is crimped.

The pump spray according to the invention has the following advantages:

- it is environmentally friendly because it contains no propellant gases,
- no allergies are induced in the user because it contains no preservatives,
- it contains no polymeric components so that no initiator molecules or catalyst residues, whose

physiological effects are unacceptable, are present,

- its storage stability is high,
- after a lengthy period of disuse or many consecutive uses, it is ensured that the amount delivered remains the same and the composition remains the same.

The beneficial properties of the pump spray according to the invention have been confirmed by pharmacokinetic investigations.

In a randomised crossover bioavailability study on 15 subjects, in each case 0.10 ml of the spray A according to the invention, of the anhydrous spray preparation B and a commercially available sublingual tablet of the same dose was administered and the blood levels were determined 1, 2, 3, 4, 5, 6, 7, 10, 20 and 30 min after administration. The commercially available Nitropen® sublingual tablet consisted of 0.3 mg of GTN and customary tablet auxiliaries. The anhydrous spray (B) had the composition 0.377% by weight glycerol trinitrate, 89.623% by weight ethanol and 10.0% by weight 1,2-propylene glycol. The spray (A) has the composition described in Example 2.

The result of the bioavailability study is listed in Table 1:

Tab. 1 - Pharmacokinetic data

	AUC [mg/ml]	c_{max} [mg/ml]	t_{max} [min]
Sublingual tablet	23.408	3.053	5.667
Spray (A) according to the invention	24.797	2.938	3.667
Anhydrous spray (B)	22.601	3.633	4.333

The shortest time for the level to rise (shortest t_{max}) in the pharmacokinetic study is achieved by spray A according to the invention, whereas the sublingual tablet showed the slowest rise in level and the longest t_{max}. Spray B, which did not contain water, lies between the two formulations.

The result of this study shows that the rate of rise in the level can in fact, surprisingly, be conically influenced by the solution properties of the formula for the agent, so that rapid relief from pain is achieved for the patient in the case of an attack.

Surprisingly, the formulation A according to the invention proved to be superior to formulation B in the function tests with commercially available pump metering atomisers:

Spray storage position	Evaporation losses over the course of 50 days at room temperature	
	Spray A according to the invention [mg]	Comparison spray B [mg]
upright	3.6 ± 3.7	30.6 ± 26.1
horizontal	12.2 ± 6.8	118.5 ± 37.6
upside down	12.1 ± 7.5	58.9 ± 30.1

Extrapolated to the shelf life of 3 years customary for a pharmaceutical, spray A according to the invention in the least favourable storage position results in an inconsiderable weight loss of about 270 mg. By contrast, comparison spray B may suffer a 2.6 g weight loss in 3 years, which reduces the shelf life of the pharmaceutical.

Sufficient stability of the pharmaceutical in terms of quality and quantity can be achieved, when the amount contained in the spray container is about 10 - 20 g of solution, only with solution A according to the invention.

Special requirements must be met by pump metering atomisers for solutions for a vital indication such as the treatment of an attack of angina pectoris: in contrast to, for example, disinfectants or the like, the availability of the dose must be ensured even after an interval after the last use of the spray. Most commercially available metering pumps must be pumped several times after a period of disuse of, in some cases, only one day because the contents of the metering chamber are

not sealed off and evaporate unhindered. It is possible to dispense with initial pumping in the case of a metering pump whose design is such that the contents of the metering chamber are sealed off.

The requirement that the full dose be administered in the first puff, irrespective of the period for which the spray has not been used after the last use, can be met with solution A according to the invention: this is because evaporation losses may occur despite closure of the metering chamber, depending on surface tension of the solution to be metered and depending on its vapour pressure and its swelling or shrinking effect on the pump components. This particularly applies to conventional spray formulations.

An investigation comparing the spray formulation A according to the invention and conventional spray formulations demonstrated that the required dose range was achieved in the first puff with the spray formulation A according to the invention even after 36 days of non-use. It amounts to 81.8% ± 6.8% of the average quantity delivered, determined on twelve (12) pump sprays.

Patent Claims

1. Hydrophilic aqueous pump spray preparation containing nitroglycerin and one or more customary auxiliaries, characterised in that the preparation contains 0.15-0.50% by weight nitroglycerin, 24.50-24.85% by weight ethanol, 32.00% by weight 1,2-propylene glycol and 43.00% by weight purified water, and is adjusted to pH 3-6.

2. Hydrophilic aqueous pump spray preparation containing nitroglycerin and one or more customary auxiliaries, according to Claim 1, characterised in that the preparation contains 0.30% by weight nitroglycerin, 24.70% by weight ethanol, 32.00% by weight 1,2-propylene glycol and 43.00% by weight purified water, and is adjusted to pH 6.0.

3. Hydrophilic aqueous pump spray preparation containing nitroglycerin and one or more customary auxiliaries, according to Claim 1, characterised in that the preparation contains 0.40% by weight nitroglycerin, 24.60% by weight ethanol, 32.00% by weight 1,2-propylene glycol and 43.00% by weight purified water, and is adjusted to pH 6.0.

4. A process for preparing a hydrophilic aqueous pump spray preparation containing nitroglycerin and one or more customary auxiliaries, according to Claim 1, characterised in that, in a conventional manner, 0.15-0.50% by weight nitroglycerin, 24.50-24.85% by weight ethanol, 32.00% by weight 1,2-propylene glycol and 43.00% by weight purified water are mixed, and the resulting

solution is adjusted to pH 3-6 and introduced into suitable primary packs.

5. A process for preparing a hydrophilic aqueous pump spray preparation containing nitroglycerin and one or more customary auxiliaries, according to Claim 4, characterised in that, in a conventional manner, 0.30% by weight nitroglycerin, 24.70% by weight ethanol, 32.00% by weight 1,2-propylene glycol and 43.00% by weight purified water are mixed, and the resulting solution is adjusted to pH 3-6 and introduced into suitable primary packs.

6. A process for preparing a hydrophilic aqueous pump spray preparation containing nitroglycerin and one or more customary auxiliaries, according to Claim 4, characterised in that, in a conventional manner, 0.40% by weight nitroglycerin, 24.60% by weight ethanol, 32.00% by weight 1,2-propylene glycol and 43.00% by weight purified water are mixed, and the resulting solution is adjusted to pH 3-6 and introduced into suitable primary packs.

7. A hydrophilic aqueous pump spray preparation according to claim 1, substantially as hereinbefore described and exemplified.

8. A process for preparing a hydrophilic aqueous pump spray preparation according to claim 1, substantially as hereinbefore described and exemplified.

9. A hydrophilic aqueous pump spray preparation according to claim 1, whenever prepared by a process claimed in a preceding claim.

Dated this the 17th day of July, 1991
F. R. KELLY & CO.

BY: _____ EXECUTIVE
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